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SYNTHESIS, CHARACTERIZATION AND ANTIMICROBIAL EVALUATION OF QUINOLONYL IMIDAZOLE DERIVATIVES

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ABSTRACT
Two series of imidazole derivatives (D_1–D_4) and (D_5–D_8) containing substituted quinolones were designed and synthesized. The chemical structures of both the series of quinolone-imidazole derivatives have been elucidated by spectral studies (IR, ^{1}H NMR and Mass spectra). The compounds were screened for their anti-bacterial activity against *Escherichia coli* ATCC 25922, *Shigella flexneri* ATCC 9199, *Staphylococcus aureus* ATCC 12600, *Bacillus cereus* ATCC 10876 by Luria Bertani (LB) media technique. Among the synthesized compounds 1-(7-hydroxy-4-methyl-2-oxoquinolin-1(2H)-yl)-4-methyl-1H-imidazole-2,5-dione (D_1) and 1-(4,7-dimethyl-2-oxoquinolin-1(2H)-yl)-4-methyl-1H-imidazole-2,5-dione (D_2) were found to show antibacterial activity against both Gram +ve and Gram –ve bacteria, indicating broad range spectrum of activity. Compounds 5,7-dihydroxy-4-methyl-1-(4-methyl-5-oxo-2-thioxo-2H-imidazol-1(5H)-yl)quinolin-2(1H)-one (D_8) and 1-(4,6-dimethyl-2-oxoquinolin-1(2H)-yl)-4-methyl-1H-imidazole-2,5-dione (D_3) was found to show antibacterial activity (zone of inhibition more than 1.0 cm) against *Escherichia coli* and *Shigella flexneri* both belonging to Gm –ve genotypes. However growth of *Bacillus cereus* (Gram +ve) was also inhibited by (D_8) and (D_3) compounds but *Staphylococcus aureus* (Gram +ve) growth was not affected, indicating narrow spectrum of antibacterial activity. All other compounds had shown mild to moderate antibacterial and antifungal activities.

KEYWORDS
Quinolone, Imidazole, Antibacterial, 1, 3 dipolar cycloaddition, Antimicrobial evaluation.

1. INTRODUCTION
Fluoroquinolones are an important kind of synthetic antibacterial agents. They exerted the powerful biological activities by primarily inhibiting the activity of type II topoisomerases or DNA gyrase to stabilize the cleavage complex at specific sites on DNA and preventing the duplication of DNA[1]. However, these drugs were largely developed for treatment of infections caused by Gram-negative bacteria, but only had limited activity against some Gram-positive bacteria. Numerous efforts have been made in order to obtain more effective derivatives with the goal of further extending the antibacterial spectrum and overcoming the

drug-resistance. Amongst, structural modification of the C–7 position in quinolone ring is the most important and meaningful strategy. It revealed that the C–7 substituents could greatly influence the inhibition of DNA gyrase and cell permeability, and ultimately impact the solubility, bioactivity, spectrum and pharmacokinetics. The increasing interest has been directing towards the structural modification at the C–7 position in quinolone ring by incorporating various types of substituents especially N-containing heterocycles like pyridine [ii], thiodiazole[iii], piperidine[iv] and triazole[v] etc.

Imidazole derivatives as antimicrobial agents have been investigated very well and shown large potentiality in medicinal chemistry[vi-vii]. Many researchers have revealed that combination of quinolone ring with other fragments is an effective strategy to overcome quinolone-resistance. Previously, various heterocycle modified quinolones as medicinal agents were widely investigated but up to now no literature has reported in the developments of N-N heterocylic fused imidazole with quinolones. So it will be interesting and rational to continue our work to combine imidazole moiety with quinolones forming N-N heterocycles. Based on this, a novel type of quinolone imidazoles were designed is a fused ring of imidazole with benzene having larger conjugated system and electron richer properties than imidazole, this unique structure endows its derivatives to possess extensive potentiality in medicinal chemistry especially antimicrobial aspect.

2. EXPERIMENTAL

2.1 Measurements

Melting Points were taken in a Buchi-545 apparatus and are uncorrected. Infra-red Spectrum was recorded on a SHIMADZU FT-IR Tracer100 spectrophotometer using direct KBr Pellets. Proton Nuclear Magnetic Resonance spectrum was recorded on a Varian Mercury YH-300 at 600 MHz spectrophotometer. Agilent 6320 (Quadrupole Mass Analyzer) spectrophotometer.

2.2 Synthesis

2.2.1. Synthesis of 1-(7-hydroxy-4-methyl-2-oxoquinolin-1(2H)-yl)-4-methyl-1H-imidazole-2,5-dione (D_1)1-(7-hydroxy-4-methyl-2-oxoquinolin-1(2H)-yl)urea (10 mmol) was charged in a 50 ml round bottom flask (RBF) containing glacial acetic acid (20 ml) fused with sodium acetate and stirred well in ethanol (10ml). Pyruvic acid (10 mmol) was charged in a stirring condition. The RBF was kept in the preheated oil bath, temperature was maintained at 120–130 °C and refluxed for a period of 5 h. Reaction mixture was cooled to room temperature, filtered using vacuum, residue was washed with ethanol 3–4 times and then dried over vacuum. This crude product was purified ethanol.

Yield: 43.67%, melting point: 214– 216 °C, I.R. (KBr) cm^{-1}: 1670, 1181, 3343, 2853, 3030, 1408, ^{1}H NMR (DMSO-d_6) δ: 6.13 (1H, d), 6.18 (1H, s), 7.05 (1H, d), 1.71 (3H, s), 5.00 (1H, s), 0.90 (3H, s), MS m/z: 285.1 (M+).
Same procedure was followed for the compounds D_1, to D_8.
2.2.2. 1-(4,7-dimethyl-2-oxoquinolin-1(2H)-yl)-4-methyl-1H-imidazole-2,5-dione (D_2)
Yield: 29.31%, melting point: 221–223 °C, I.R. (KBr) cm^{-1}: 1650, 1173, 3358, 2869, 3029, 1603, ^{1}H NMR ($CDCl_3$) δ: 6.46 (1H, d), 6.41 (2H, s,) 7.12 (1H, d), 1.73 (3H, s), 2.35 (3H, s), 0.93 (3H, s), MS m/z: 283.1 (M+).
2.2.3. 1-(4,6-dimethyl-2-oxoquinolin-1(2H)-yl)-4-methyl-1H-imidazole-2,5-dione (D_3)
Yield: 25.02%, melting point: 199–203 °C, I.R. (KBr) cm^{-1}: 1669, 1201, 3318, 2853, 1230,

2817, 1417, ^{1}H NMR ($CDCl_3$) δ: 6.86 (1H, d), 6.49 (1H, s), 7.02 (1H, d), 1.71 (3H, s) 2.46 (3H, s) 6.35 (1H, s) MS m/z: 283.0 (M+).

2.2.4. 1-(5,7-dihydroxy-4-methyl-2-oxoquinolin-1(2H)-yl)-4-methyl-1H-imidazole-2,5-dione (D_4)

Yield: 43.37%, melting point: 221–223 °C, I.R. (KBr) cm^{-1}: 1645, 1160, 3326, 2867, 1323, 2762, 1399, ^{1}H NMR (DMSO-d_6) δ: 5.60 (1H, s), 5.64 (1H, s), 1.71 (3H, s), 5.20 (H, s), 1.13 (3H, s), 5.00 (1H, s), 6.35 (1H, s), MS m/z: 301 (M+).

2.2.5.7-hydroxy-4-methyl-1-(4-methyl-5-oxo-2-thioxo-2H-imidazol-1(5H)-yl)quinolin-2(1H)-one (D_5)

Yield: 28.33% melting point: 219–223 °C, I.R. (KBr) cm^{-1}: 1667, 1182, 3343, 2853, 3030, 2924, 1402, ^{1}H NMR (DMSO-d_6) δ: 6.13 (1H, d), 6.08 (1H, s), 7.05 (1H, d), 1.71 (3H, s), 5.05 (1H, s), 0.95 (3H, s), 6.35 (1H, s) MS m/z: 301.1 (M+).

2.2.6. 4,7-dimethyl-1-(4-methyl-5-oxo-2-thioxo-2H-imidazol-1(5H)-yl)quinolin-2(1H)-one (D_6)

Yield: 37.05%, melting point: 224–227 °C, I.R. (KBr) cm^{-1}: 1666, 1170, 3258, 2860, 3029, 1410, 3469, 1266, ^{1}H NMR ($CDCl_3$) δ: 6.46 (1H, d), 6.41 (1H, s), 7.10 (1H, d), 1.71 (3H, s), 2.35(3H, s), 6.35 (1H, s) 0.95 (3H, s) MS m/z: 299.0 (M+).

2.2.7. 4,6-dimethyl-1-(4-methyl-5-oxo-2-thioxo-2H-imidazol-1(5H)-yl)quinolin-2(1H)-one (D_7)

Yield: 27.49%, melting point: 218–220 °C, I.R. (KBr) cm^{-1}: 1665, 1173, 3263, 2862, 3029, 1410, 3469, 1266, ^{1}H NMR ($CDCl_3$) δ: 6.86 (1H, d), 6.49 (1H, s), 7.02 (1H, d), 1.71 (3H, s), 2.35 (3H, s), 6.35 (1H, s), 0.90 (3H, s). MS m/z: 299.07 (M+).

2.2.8. 5,7-dihydroxy-4-methyl-1-(4-methyl-5-oxo-2-thioxo-2H-imidazol-1(5H)-yl)quinolin-2(1H)-one (D_8)

Yield: 34.02%, melting point: 226–229 °C, I.R. (KBr) cm^{-1}: 1679, 1180, 3396, 2873, 3032, 1410, 3469, 1266, ^{1}H NMR (DMSO-d_6) δ: 5.60 (1H, s), 5.64 (1H, s), 1.71 (3H, s), 5.00 (1H, s), 1.35 (3H, s), 6.35 (1H, s), 5.00 (1H, s). MS m/z: 317.0 (M+).

2.3. Anti-microbial screening

The bacterial strains studied are identified strains and were purchased from the Hi-media Pvt. Ltd. culture collection, Mumbai. The investigated microorganisms were *Escherichia coli* ATCC 25922, *Shigella flexneri* ATCC9199, *Staphylococcus aureus* ATCC 12600, *Bacillus cereus* ATCC10876. All four bacterial strains used were common food borne pathogens, including two Gram –ve bacteria such as *Escherichia coli* ATCC 25922 & *Shigella flexneri* ATCC9199, and two Gram +ve bacteria such as *Staphylococcus aureus* ATCC 12600 & *Bacillus cereus* ATCC 10876.

2.3.1. Preparation of the test compound

The compounds were dissolved at a concentration of 1.0 mg/ml in Di-Methyl Forma-amide (DMF). The synthesized compounds are soluble only in DMF.

2.3.2. Minimum inhibitory concentration (MIC)

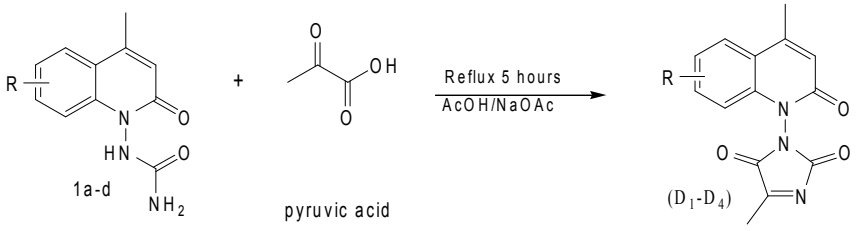
A loop full of the given test strain was inoculated into 25 ml of Luria Bertani broth (LB Broth) and incubated for 24 h in an incubator at 37^{o}C in order to activate the bacterial strain. A petri dish of 100 mm diameter was filled with 28-30 ml of Luria Bertani (LB) media. Inoculation was performed by the pour plate technique. 0.2 ml of the activated strain was inoculated into the media when it had reached a temperature of 40-45^{o}C. The complete procedure of the ditch preparation was done in a laminar airflow to maintain strict sterile and aseptic condition. The media was allowed to solidify. After solidification of the media, a well was made in the media with help of a cup-borer (0.5 cm) and then 0.03 ml of the synthetic

compound (dissolved in DMF) was inoculated into the well. Controls were performed (for each bacterial strain), where 0.03 ml of the pure solvent was inoculated into each well. The plates were incubated for 24 h at 37^{o}C. The inhibition zone formed by the compounds against the particular test bacterial strain determined the antibacterial activities of the synthetic compounds. The observed inhibition zone is presented in Table 1.

3. RESULTS AND DISCUSSION

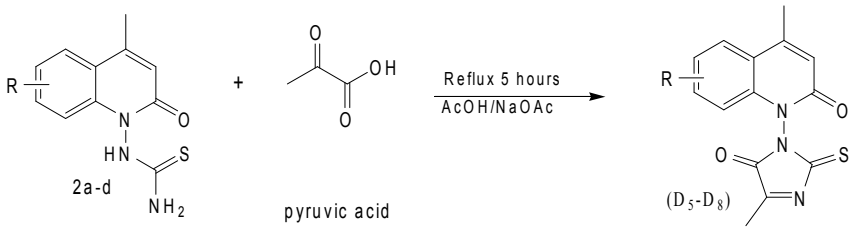
3.1. Chemistry

In this present investigation a novel series of substituted quinolonyl imidazole compounds were synthesized as per Schemes 1–2. Scheme 1 illustrates the pathway used for the synthesis of Quinolonyl imidazole. [1-(substituted-4-methyl-2-oxoquinolin-1(2H)-yl)-4-methyl-1H-imidazole-2,5-dione] (D_1 -D_4) was obtained by treating 1-(substituted-4-methyl-2-oxoquinolin-1(2H)-yl)urea (1a-d) with pyruvic acid and glacial acetic acid fused with sodium acetate. Scheme 2 shows the reaction between 1-(substituted-4-methyl-2-oxoquinolin-1(2H)-yl)thiourea (2a-d) and with pyruvic acid and glacial acetic acid fused with sodium acetate which gives substituted (4-methyl-5-oxo-2-thioxo-2H-imidazol-1(5H)-yl)quinolin 2(1H)-one (D_5-D_8). The mechanism of reaction involves 1, 3 dipolar cycloaddition between the compounds (1a-d)/(2a-d) and pyruvic acid to give N-N bicyclic product (D_1-D_8).



R = 7-OH; 7-CH_3; 6-CH_3; 5, 7–di-OH in the compounds D_1 to D_4 respectively.

Scheme 1



R = 7-OH; 7-CH_3; 6-CH_3; 5, 7–di-OH in the compounds D_5 to D_8 respectively.

Scheme 2

The structures of the compounds were characterized by IR, ^{1}H NMR and Mass spectral data. IR spectra of the compounds showed CO stretching at 1645– 1680 cm^{-1}due to

conjugation. In ^{1}H NMR spectra, the quinolonyl imidazole compounds showed the methyl proton of imidazole at 0.9 ppm as a singlet, quinolone Ar–H protons as doublet at 6.13–7.02 ppm in (D_2,D_3,D_6,D_7) while singlet at 5.60-5.64 ppm in (D_4,D_8), methyl proton of at the range 1.71-1.75 ppm and proton of ethene at 6.35 ppm. In mass analysis all the compounds have M+1 ion peaks.

3.2. Biological investigation

The inhibition zone formed by the compounds against the particular test bacterial strain determined the antibacterial activities of the synthetic compounds. Test compounds viz; D_1 and D_2 were found to show antibacterial acitivity against both Gram +ve and Gram –ve bacteria, indicating broad range spectrum of activity. Compound D_7 and D_8 was found to show antibacterial activity (zone of inhibition more than 1.0 cm) against *Escherichia coli* and *Shigella flexneri* both belonging to Gm –ve genotypes. However growth of *Bacillus cereus* (Gram +ve) was also inhibited by D_3 compound but *Staphylococcus aureus* (Gram +ve) growth was not affected, indicating narrow spectrum of antibacterial activity. Other compounds viz; D_4, D_5 and D_6 showed variable antibacterial activity.

Table 1 Anti-microbial activity of the synthesized compounds.

Compound	*In vitro* activity – zone of inhibition in mm (MIC in lg/ml)			
	E.coli ATCC 25922	*S.flexneri* ATCC 9199	*S. aureus* ATCC 12600	*B.cereus* ATCC 2853
D_1	++	+	++	+
D_2	++	+	++	+
D_3	++	++	-	++
D_4	++	-	+	+
D_5	+	-	++	+
D_6	++	-	+	+
D_7	++	+	-	+
D_8	++	++	-	+

++ zone of inhibition (0. 5 -1.5 cm diameter); + zone of inhibition (>1.0 cm diameter);

- no zone of inhibition

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